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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/940,860	08/29/2001	Richard E. Rothman	001107.00185	5063

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BANNER & WITCOFF  
1001 G STREET N W  
SUITE 1100  
WASHINGTON, DC 20001

EXAMINER

CHUNDURU, SURYAPRABHA

ART UNIT	PAPER NUMBER
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1637

DATE MAILED: 02/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b> 09/940,860	<b>Applicant(s)</b> ROTHMAN ET AL.	
	<b>Examiner</b> Suryaprabha Chunduru	<b>Art Unit</b> 1637	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 02 December 2004.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 2-23 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 2-23 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

**DETAILED ACTION**

1. Applicants' response to the previous office action filed on December 2, 2004 has been entered.
2. Claims 2-23 are pending. Claims 2, 7, and 23 are amended. Claims 1, 24-32 are cancelled.
3. This application is field on August 29, 2001, which claims the benefit of US provisional application 60/229,376 filed on August 31, 2000.

***New Grounds of Rejections***

4. Claim 2 is objected because of the following informalities:

Claim 2 recites 'pair of primers *have has*'. Correction is required.

***Claim Rejections - 35 USC § 112***

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

A. Claims 2-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 2 recites "have has". The meets and bounds of the claim are unclear and vague because it is not clear whether a primer of the primer pair has no restriction sites for the restriction endonuclease or both the primers of the primer pair have no restriction sites.

B. Claims 7 and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The instant claim 7 recites primers "having sequences as shown " and claim 23 recites 'primers having sequences selected from the group consisting of'.

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It is unclear whether the term "having" represents primers consist of the said sequences or primers comprising of said sequences.

*Claim Rejections - 35 USC § 103*

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

A. Claims 2, 4-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoshina et al. (USPN. 5,571,674) in view of Dougherty et al. (J Virol. Methods., Vol. 41, pages 235-238, 1993).

Hoshina et al. teach a method of claim 2, of performing polymerase chain reaction (PCR) comprising

Mixing test sample and the PCR reagents, which include a primer pair to form a mixture (see col. 7, line 21-29, col. 17, line 66-67, col. 18, line 22-25) and subjecting the mixture to

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conditions such that any templates present in the test sample which hybridizes to said primer pair are amplified and detecting amplification product (see col. 7, line 29-37, col. 18, line 22-28).

With regard to claim 5, 11, Hoshina et al. teach that said sample is a treated blood sample and said treatment comprises extracting DNA therefrom (see col. 18, line 35-40, col. 7, line 21-29);

With regard to claim 6, Hoshina et al. teach that said blood sample from patients suspected of systemic bacteremia (see col. 20, line 22-53);

With regard to claim 7, Hoshima et al. teach primer sequence having (considered as open language as “comprising”) the sequence as claimed in SEQ ID 1 (see sequence alignment).

With regard to claims 9-10, Hoshina et al. teach that said detection step employs gel electrophoresis and the amplification product is labeled with ethidium bromide and visualized under ultraviolet light (see col. 7, line 34-37);

With regard to claims 12-13, Hoshina et al. teach that said sample is obtained from urine and cerebrospinal fluid (See 18, line 35-43);

With regard to claims 14-15, Hoshina et al. teach that the development of primers hybridize to at eubacterial species' DNA in regions which are highly conserved and comprises 16S RNA genes (see col. 15, line 59-67, col. 16, line 1-6, col. 18, line 25-28, Figs.12-16);

With regard to claims 16-17, 21-22, Hoshina et al. also teach that the method further comprises identifying the bacterial species by sequencing the amplification product or by using restriction endonuclease digestion or restriction mapping that indicates use of one or more restriction endonucleases (see col. 7, line 34-52);

With regard to claim 18, Hoshina et al. teach that said method further comprises identifying a bacterial species by amplification of amplified product or amplification of templates in a test sample using primers selected from a single eubacterial species 16S RNA (see col. 19, line 54-67, col. 20, line 1-3, col. 21, line 23-43);

However, Hoshina et al. did not teach digesting PCR mixture comprising Taq polymerase, deoxynucleotides (dNTPs), reaction buffer and a pair of primers using a restriction enzyme, that do not cleave said pair of primers.

Dougherty et al. teach a method of claim 2, for PCR amplification comprising pretreatment of PCR cocktail mixture comprising reaction buffer, dNTPs, primers and Taq DNA polymerase (see page 236, paragraph 2 under materials and methods section).

With regard to claims 2, 4, 8, Dougherty et al. teach pretreatment of PCR cocktail mixture with a restriction endonuclease and inactivating the restriction enzyme at 96<sup>0</sup> C (see page 237, paragraphs 2-3 under results and Discussion section, Fig. 1, page 235, abstract). Dougherty et al. also teach use of restriction enzymes that do not cut within the primer binding sites and also disclose that restriction endonucleases generally react with specific double-stranded sequence and are inefficient in action on equivalent single-strand sequences (see page 236, paragraph 2).

Therefore, it would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made, to combine the method of amplification of a target nucleic acid as taught by Hoshina et al. with the step of digesting PCR reaction mixture a restriction endonuclease before PCR reaction as taught by Dougherty et al. to achieve expected advantage of developing a sensitive and enhanced method for amplification of a specific target. An ordinary

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skill in the art would have reasonable expectation of success that digesting PCR reaction mixture with a restriction endonuclease before PCR would result in enhancing the yield of specific PCR product because Dougherty et al. have explicitly showed that digesting the PCR reaction mixture with a restriction enzyme that do not cut within the primer binding sites before PCR amplification reduces false-positive signals and enhances the amplification of specific PCR product(s) (see page 235, abstract). Therefore an ordinary practitioner would have been motivated to combine the method of Hoshina et al. with the inclusion of pre-digestion of PCR reaction mixture before PCR as taught by Dougherty et al. to develop a sensitive and enhanced method for amplification of a specific target PCR product.

B. Claim 3, 23 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hoshina et al. (USPN. 5,571,674) in view of Dougherty et al. (J Virol. Methods., Vol. 41, pages 235-238, 1993) as applied to claims 2, 4-6, 9-22 above, and further in view of Stratagene Catalog (Stratagene Catalog, page 301-303, 306-308, 1995).

Hoshina et al. in view of Dougherty et al. teach a method for in amplification of a target nucleic acid as discussed in the above section 6A.

Neither Hoshina et al. nor Dougherty et al. teach specifically said restriction endonuclease as Alu I.

Stratagene catalog discloses Alu I (AG/CT) cleaves the double strand sequences to make blunt end fragments as Sma I (CCC/GGG) (see page 301-303) and both enzymes are involved in site-specific methylation (page 306-308).

Therefore, it would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made, to combine the method of amplification of a target nucleic

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acid as taught by Hoshina et al. in view of Dougherty et al. with the use of specific restriction endonuclease such as Alu I as taught by Statagene Catalog to achieve expected advantage of developing a sensitive and enhanced method for amplification of target DNA cells. An ordinary skill in the art would have had a reasonable expectation of success that digestion of PCR reaction mixture with Alu I before PCR amplification as taught by Hoshina et al. in view of Dougherty et al. would result in an enhanced sensitive detection assay because Stratagene Catalog discloses Alu I has similar activities both in forming blunt-end fragments and site-specific methylation activity with Sma I and therefore these restriction enzymes are considered as equivalents. The ordinary artisan would have been motivated to use several such restriction enzymes and such restriction enzymes are considered functionally equivalent to the claimed restriction enzyme in the absence of secondary considerations.

Further, it would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made, to use the sequences comprising conserved eubacterial 16S RNA region as taught by Hoshina et al to generate primer pairs to amplify and detect target bacterial nucleotide sequence because Hoshina et al. taught generating such primer pairs using 16S RNA region to amplify species-specific target nucleic acids (see col. 4, Fig. 7). The ordinary artisan would have been motivated to generate a number of primer pairs for detection of target 16S RNA region, such primers and primer pairs are considered functionally equivalent to the claimed primer pairs in the absence of secondary considerations.

### ***Conclusion***


No claims are allowable.


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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suryaprabha Chunduru whose telephone number is 571-272-0783. The examiner can normally be reached on 8.30A.M. - 4.30P.M , Mon - Friday,.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

  
Suryaprabha Chunduru  
Examiner  
Art Unit 1637

  
JEFFREY FREDMAN  
PRIMARY EXAMINER  
2/5/05